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(54) **DISPOSABLE TANGENTIAL FLOW
FILTRATION LINER WITH SENSOR MOUNT**

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See application file for complete search history.

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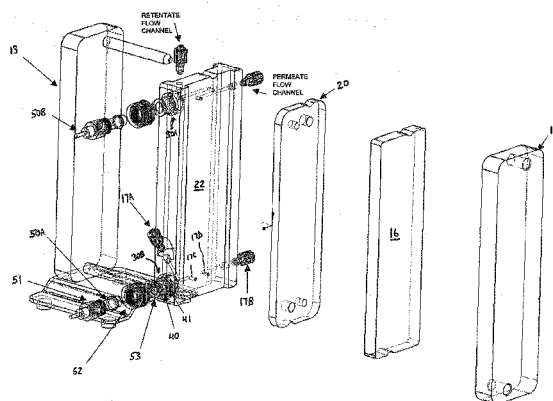
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(57) **ABSTRACT**

Tangential flow filtration device is provided wherein liners
are provided between the filtration element and the top and
bottom holders or manifolds. The liners incorporate the flow
channels and inlet and outlet ports, as well as a sensor mount.
The liners are made of an inexpensive material and therefore
are disposable after a single use, making it more cost effective
to dispose of them than to clean the conventional manifolds.
The sensor mount accommodates a removable sensor, and
isolates it from the fluid path.

5 Claims, 3 Drawing Sheets



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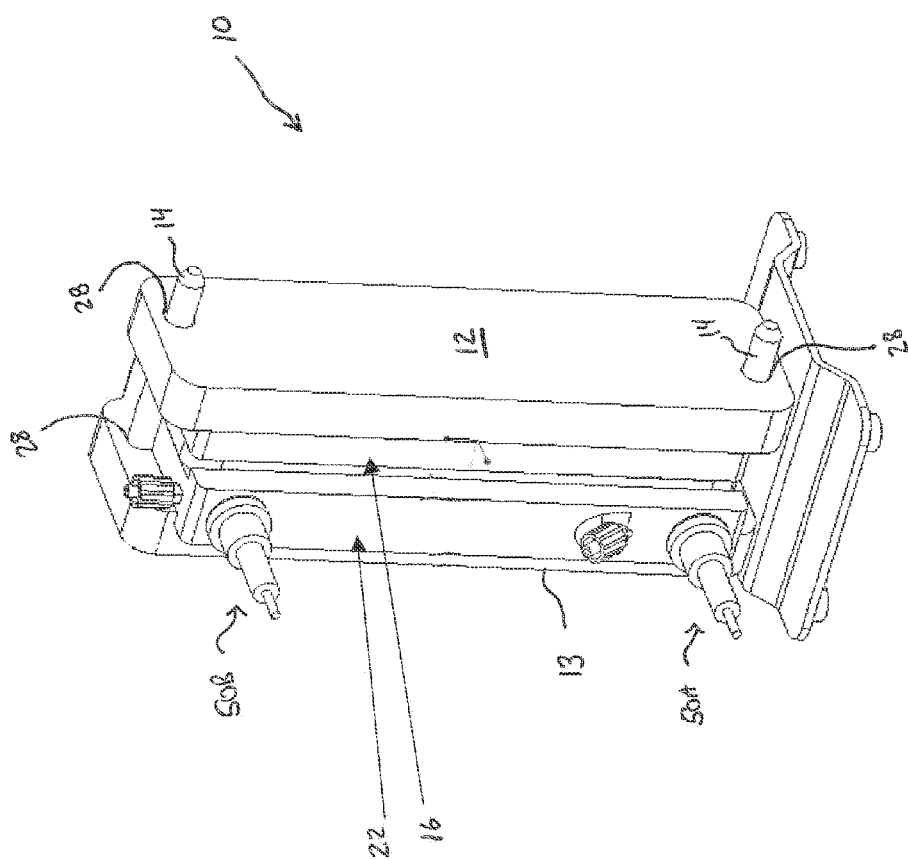


FIG. 1

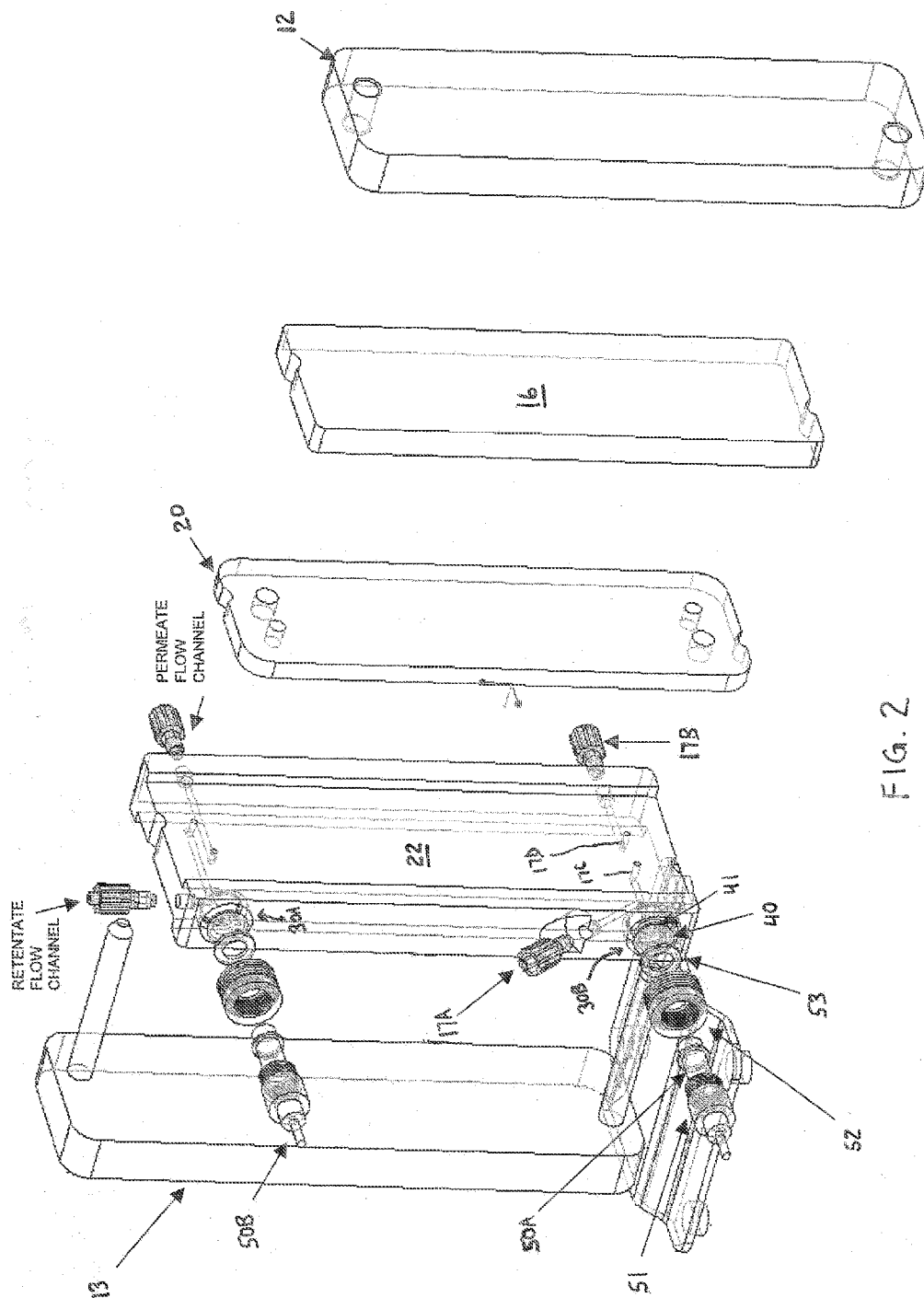
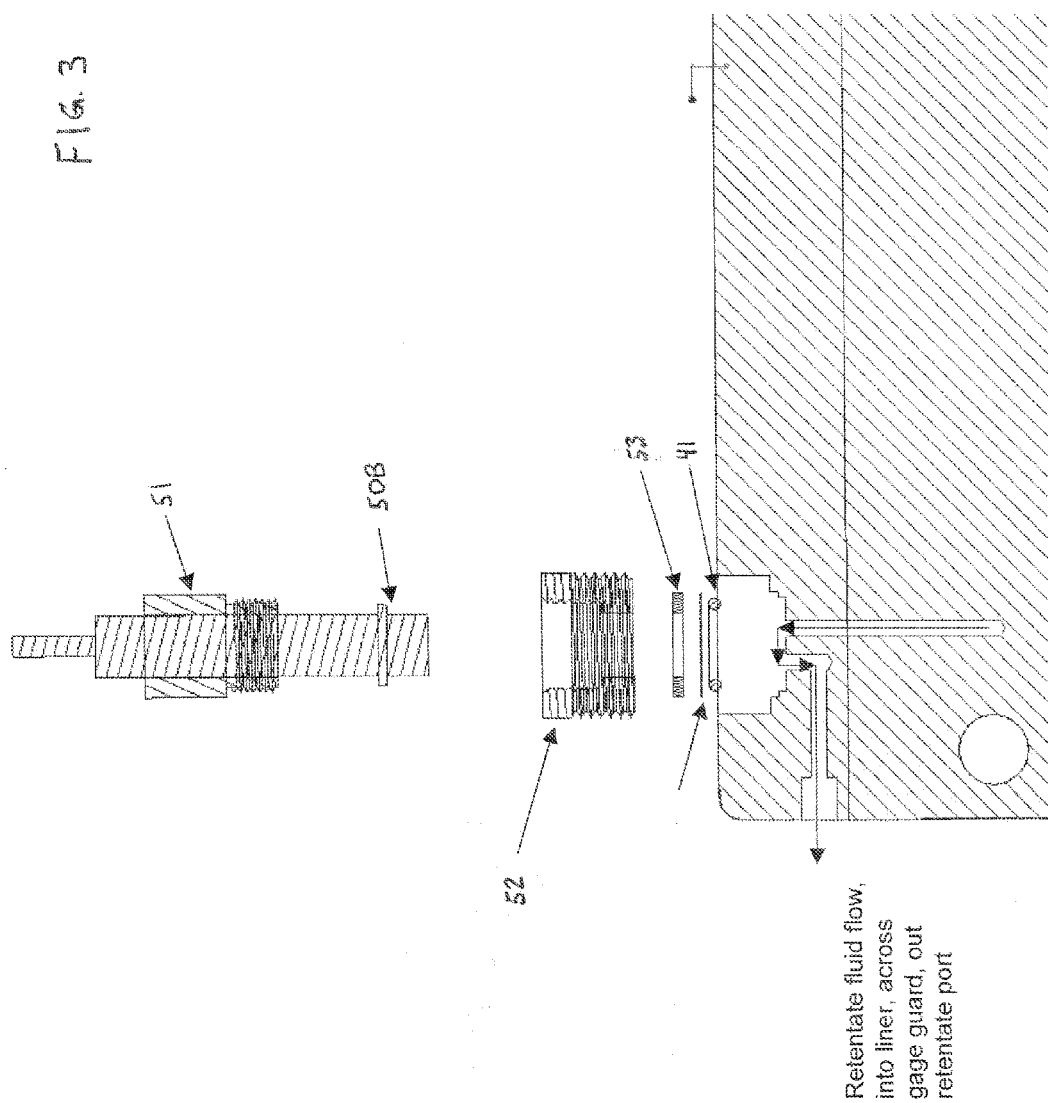


FIG. 2



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DISPOSABLE TANGENTIAL FLOW FILTRATION LINER WITH SENSOR MOUNT

This application is a divisional of U.S. patent application Ser. No. 12/784,094 filed May 20, 2010, which claims priority of U.S. Provisional Application Ser. No. 61/217,323 filed May 29, 2009, the disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Tangential Flow Filtration (TFF) is a separation process that uses membranes to separate components in a liquid solution or suspension on the basis of size or molecule weight differences. Applications include concentration, clarification, and desalting of proteins and other biomolecules such as nucleotides, antigens, and monoclonal antibodies; buffer exchange; process development; membrane selection studies; pre-chromatographic clarification to remove colloidal particles; depyrogenation of small molecules such as dextrose and antibiotics; harvesting, washing or clarification of cell cultures, lysates, colloidal suspensions and viral cultures; and sample preparation.

In TFF, the solution or suspension to be filtered is passed across the surface of the membrane in a cross-flow mode. The driving force for filtration is the transmembrane pressure, usually created with a peristaltic pump in disposable TFF applications. The velocity at which the filtrate is passed across the membrane surface also controls the filtration rate and helps prevent clogging of the membrane. Because TFF recirculates retentate across the membrane surface, membrane fouling is minimized, a high filtration rate is maintained, and product recovery is enhanced.

Conventional TFF devices are formed of a plurality of elements, including a pump, a feed solution reservoir, a filtration module and conduits for connecting these elements. In use, the feed solution is directed from the feed solution reservoir to the filtration module while the retentate from the filtration module is recirculated from the filtration module to the feed solution reservoir until the desired volume of retentate is obtained. The membrane is sandwiched between top and bottom manifolds or holders, which serve to provide accurate mechanical constraint against the internal hydraulic pressure of the device, and also serve to distribute the filtration stream across the multiple flow paths within the device. These manifolds or holders are typically made of stainless steel and must be cleaned and validated prior to each use, particularly in biopharmaceutical and other sanitary applications. This is an expensive and time-consuming process.

Where cleaning and validation steps are desired to be eliminated when replacing the filtration medium, disposable liners can be used instead of the reusable stainless steel liners. The liners incorporate the flow channels and inlet and outlet ports that were previously present in the manifolds, and isolate the process fluid from coming into contact with the TFF holder. The liners can be made of an inexpensive material and therefore are disposable after a single use, making it more cost effective to dispose of them than to clean the conventional manifolds. In addition, the liners can be pre-sterilized. In order to provide sufficient strength and rigidity under operating conditions, the liners can have a grid pattern of ribs that abut the holder plates to help prevent the liners from torquing under clamping force.

It also would be desirable to incorporate sensors in the liners, for measuring various process parameters, such as

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pressure, without having to clean or sterilize the sensors when replacing the filtration medium and/or liners.

SUMMARY OF THE INVENTION

The shortcomings of the prior art are overcome by the embodiments disclosed herein, which include a tangential filtration assembly including one or more preferably disposable liners having one or more sensors disposed therein. The sensor(s) are isolated from the fluid and are removable from the liner. As a result, after use the liner can be disposed and the sensor(s) reused without having to clean the sensor.

In accordance with certain embodiments, a tangential flow filtration device is provided wherein one or more liners are located between the filtration element and the top and bottom holders or manifolds. The liners incorporate the flow channels and inlet and outlet ports that are conventionally present in the stainless steel manifolds. The liners are made of an inexpensive material and therefore are disposable after a single use, making it more cost effective to dispose of them than to clean the conventional manifolds. In addition, the liners can be pre-sterilized. In order to provide sufficient strength and rigidity under operating conditions, the liners can have a grid pattern of ribs that abut the holder plates to help prevent the liners from torquing under clamping force.

The one or more liners includes one or more sensor ports or mounts, for removably affixing a sensor to the liner. A diaphragm is disposed between the sensor and the fluid passageway in the liner, isolating the sensor components from directly contacting fluid in the passageway. The sensor remains capable of sensing the pressure of the fluid in the passageway, but the presence of the diaphragm prevents the sensor from being contaminated by the fluid.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is perspective view of a tangential flow filtration assembly in accordance with certain embodiments;

FIG. 2 is an exploded view of the assembly of FIG. 1; and

FIG. 3 is an exploded view showing a sensor and a sensor port in accordance with certain embodiments.

DETAILED DESCRIPTION OF THE INVENTION

Turning first to FIG. 1, there is shown a filtration device in accordance with certain embodiments. The device 10 includes a top holder plate 12 and a spaced bottom holder plate 13. The holder plates 12, 13 are preferably made of stainless steel and are sufficiently rigid and durable to provide accurate and effective mechanical constraint of the assembly against internal hydraulic operating pressures, such as 50-60 psi. Apertures 28 are provided in the holder plates 12, 13 and in each layer of the assembly to accommodate tie rods or threaded pins or bolts 14 or other clamping device to secure the assembly together. Spacers (not shown) can be provided, and can be spring-loaded. No filtration stream passageways are present in the holder plates 12, 13.

Positioned beneath holder plate 12 in the assembled state is disposable liner 16. The liner 16 is preferably made of inexpensive material, suitable for the application, that is acceptable for the particular assay, such as pharmaceutical assays, (and preferably is government approved). Suitable materials of construction include plastics, such as polystyrene, preferably polyolefins, such as polypropylene, polyethylene, copolymers and mixtures thereof. Polysulfone is particularly preferred in view of its strength and rigidity. The liner 16 is

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preferably molded with passageways and openings. Alternatively, and less preferred, it may be formed by milling, drilling and other such methods.

A filtration element **20** is sandwiched between liner **16** and a second disposable liner **22**. The filtration element **20** can be a single membrane, and is preferably a plurality of stacked membranes, such as stacked ultrafiltration or microfiltration membranes, most preferably provided in the form of a cassette. Although a single cassette of membranes is shown, those skilled in the art will appreciate that multiple cassettes can be used. Suitable cassettes are sold under the name PELLICON® and are commercially available from Millipore Corporation.

As is conventional in the art, the liner **22** includes a first port **17A**, one or more sub-ports **17C**, a second port **17B** and one or more sub-ports **17D** (FIG. 2). Port **17A** is for introduction of feed or removal of retentate, depending on its orientation within the assembly, with port **17B** for removal of permeate, while preventing admixture of the filtrate with the retentate or feed, as is conventional. Port **17A** is in fluid communication with the one or more sub-ports **17C**. Port **17A** is in fluid communication with **17C** and with the sensor port closest to it. Port **17A** also is in fluid communication with the feed port of the cassette, e.g., a PELLICON® cassette. Port **17B** is in fluid communication with the one or more sub-ports **17D**. Port **17B** is only in communication with **17D** and the permeate drain port of the cassette. The ports **17A** and **17B** may be located on opposite sides of the liner in order to provide adequate spacing and avoid interferences with other components. However, where spacing is sufficient or no interference occurs, they may be located on the same side. Each port **17A**, **17B** is in fluid communication with flow paths or passageways in the liner body that communicate with respective apertures to accommodate flow of feed, retentate or permeate as is conventional, thereby defining multiple flow paths for the filtration stream within the device.

The passageways can be tapered, narrowing as they proceed away from their respective port, to normalize pressure at each of the sub-ports **17C** and **17D**.

In certain embodiments, one side of one or both of the liners **16**, **22** can include a plurality of inter-engaging ribs. The ribs provide added rigidity to the liners, and can be formed in the molding process. The ribs, when present, are positioned on the side of the liner that contacts the holder plate **12** or **13**. The ribs extend from one side of the liner to the other, except where interrupted by a port. When assembled, there is significant clamping force applied to the filter element **20** and the liner, with sealing taking place between the smooth side of the liner **16**, **22** and the filter element **20**. The ribs assist in effectively assemble the liners in the filtration device of the invention, in sealing engagement upon the application of pressure, without the necessity of having corresponding grooves in the holder plates to mate with the ribs. Accordingly, the respective surfaces of the holder plates that abut the grids of the liners can be flat, and need not be specially designed to fit the liners.

In certain embodiments, one or more sensors, preferably two sensors such as feed pressure sensor **50A** and retentate pressure sensor **50B**, are removably connected to mount ports in one or more of the disposable liners. For purposes of illustration, two ports **30A**, **30B** are shown in liner **22**. The port or ports **30A**, **30B** are each positioned to communication with a fluid path, so that a characteristic of the fluid in the fluid path (e.g., pressure) can be measured. A membrane or diaphragm **40**, such as a diaphragm made of PVDF or polyolefin, preferably polyethylene, for example, is positioned over the port **30A** (or **30B**) in order to isolate, during operation, fluid in

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the fluid path from the sensor components. An O-ring **41** or the like can be used to seal the diaphragm **40** to the port. The membrane or diaphragm can be permanently attached to the port if desired.

In certain embodiments, the sensors are attached to the liner **22** using a diaphragm compression nut **52**, as best seen in FIGS. 2 and 3. The nut **52** is internally threaded, the internal threads corresponding to external threads on a sensor compression nut **51** positioned on the sensor **50A** so that the sensor **50A** may be screwed into the nut **52**. The sensor compression nut **51** compresses the sensor flange into the larger diaphragm compression nut **52**. The nut **52** is also externally threaded, the external threads corresponding to threads in the port **30B** so that the nut **52** may be screwed into the port. A slip washer **53** can be positioned between the compression nut **52** and the diaphragm as shown. The nut **52** compresses the O-ring **41**, diaphragm **40** and washer **53** in place. Those skilled in the art will appreciate that other means of attaching the sensor to the mount port can be used, such as a press fit into the port or a suitable receptacle affixed to the port, clamps or fasteners that hold the sensor in place, etc.

In the assembled condition, the operative portion of the sensor is positioned directly against the membrane or diaphragm. The membrane or diaphragm is made of a sufficiently flexible material so that it deflects in response to pressure, remains continuous and does not break or lose the ability to isolate the sensor from the fluid path. The membrane or diaphragm can be semi-permeable or non-permeable. It is preferably of sterilizing grade.

The presence of two sensors **50A**, **50B**, one measuring feed pressure and the other retentate pressure, allows the transmembrane pressure to be calculated, as transmembrane pressure is the average of the feed and retentate pressures less the filtrate pressure. The filtrate pressure can be determined in a conventional manner well known to those skilled in the art. In use, the removable sensors are preferably in electrical communication with a control unit, which can record the relevant process parameters, such as feed pressure, retentate pressure, transmembrane pressure, etc., and can control the parameters accordingly.

By removably connecting the sensors to the mount ports on the disposable liner(s) in accordance with the embodiments disclosed herein, the sensors remain isolated from the fluid paths and can be readily removed from the liners and reused, while the liners can be discarded after use. This results in quick and easy system set up.

The length of the ports **30A** and **B** are such that preferably there is little or no deadleg between the diaphragm of the sensor port and the conduit in which the fluid to be sensed passes. This ensures that no fluid is lost or becomes stagnant.

Suitable sensors include electromechanical sensors, due to cost, accuracy, reliability and availability concerns. Electromechanical sensors include a strain gauge bonded to a thin metal diaphragm. Deformation of the diaphragm results in deformation of the strain gauge, sending a proportional electrical signal to the control unit. Those skilled in the art will appreciate that sensors that operate using different technologies also could be used.

What is claimed is:

1. A method of filtering a sample, comprising: providing a top plate, a bottom plate spaced from said top plate, a filtration member positioned between said top plate and said bottom plate, and at least one disposable liner positioned between said top plate and said filtration member, said liner having a fluid inlet, a fluid outlet, at least one fluid path within said liner, and a sensor port in fluid communication with said fluid path;

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sealing a diaphragm to said sensor port;
attaching a sensor to said sensor port such that said diaphragm isolates said sensor from direct contact with fluid in said fluid path when fluid is in said fluid path;
introducing a fluid sample to be filtered into said filtration apparatus; and
sensing pressure in said at least one fluid path with said sensor through said diaphragm.

2. The method of claim 1, further comprising providing at least a second fluid path, a second sensor port, and a second diaphragm sealed to said second sensor port in said liner, and removably connecting a second sensor to said second sensor port for sensing pressure in said second fluid path through said second diaphragm without contacting fluid in said second fluid path.

3. The method of claim 1, further comprising removing said sensor from said sensor port, said sensor being free from contamination by said fluid not requiring cleaning.

4. The method of claim 1, wherein said diaphragm comprises PVDF or polyethylene.

5. The method of claim 1, wherein said diaphragm is semi-permeable.

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